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THE ROLE OF THE MUSCULOSKELETAL SYSTEM IN POST-BURN HYPERMETABOLISM

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Abstract

Burn injury results in a triad of inter-related adaptive responses: a systemic inflammatory response, a stress response, and a consequent hypermetabolic state which supports the former two. Details of what precisely triggers these responses as well as the sequence of events leading up to these responses are not clear. We review the musculoskeletal effects of burn injury to determine the precise contributions of this system in the generation and sustenance of this post-burn triad as well as the possible effects of pharmacologic intervention in the musculoskeletal response to burns on the resulting hypermetabolism. Inflammation-associated bone resorption liberates calcium, which may either prolong or intensify the systemic inflammatory response. Phosphate and magnesium liberated from bone could contribute to sustaining the increased ATP turnover in skeletal muscle that accompanies burn hypermetabolism. Reduced bone formation resulting from both pro-inflammatory cytokines and elevated endogenous glucocorticoid production results in reduced bone mass and therefore reduced osteocalcin production, which may contribute to reduced glucose uptake by skeletal muscle. Moreover, bone resorption liberates muscle catabolic factors such as transforming growth factor β , which contribute to the muscle wasting of burn hypermetabolism. Pharmacologic intervention with anti-resorptive agents early in the process preserve bone and muscle mass post-burn and future research should address the consequences for the hypermetabolic triad duration and intensity accompanying burn injury.

Keywords

hypermetabolism; burn injury; bone; muscle

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Declarations

The author reports one potential conflict of interest in the preparation of this manuscript. On 10 April 2019 he gave a talk at a pediatric endocrinology conference at Boston Children's Hospital hosted by a member of the Metabolism Editorial Board (CMG) for which he will receive an honorarium of \$500.

1. Introduction

Severe burn injury is one generally agreed to involve at least 30% of body surface area (1). It is an important category because individuals with severe burns have an associated hypermetabolism, resulting in prolonged catabolic effects on the body, including growth failure in children (2) that can last for at least a year following discharge from hospital. Rehabilitation, especially from the loss of muscle mass, is also prolonged and can take up the entire first year or longer following the injury. Also of note is that morbidity and mortality from burn injury are greater in adults than in children with the same extent of burn (3). We will explore possible reasons for this observation below. Burn injury represents the fourth leading cause of death among children in the United States, according to the World Health Organization (4) and in 2008, the WHO records that over 410,000 burn injuries occurred in the United States alone and that 40,000 of them required hospitalization (5).

Severe burn injury results in a hypermetabolic/catabolic state that is intimately associated with both a systemic inflammatory response and a stress response, the latter including the robust and sustained endogenous production of both glucocorticoids and catecholamines (6). Many of the intermediate steps in the pathogenesis of these three associated conditions are still unclear. These include the signals from the inflammatory response that trigger hypermetabolism and the exact sequence of post-burn events leading to the acute onset of this triad. One area that has so far not factored into the explanations for the pathogenesis of these conditions is the contribution of the musculoskeletal system to this abnormal situation. The current review adds the musculoskeletal dimension to the pathophysiology of the post-burn state and discusses possible musculoskeletal interventions that may ameliorate this triad. The features of these three associated conditions are given in Table 1 below.

2. The Systemic Inflammatory Response

Whether or not one calls this a syndrome, the inflammatory response following a burn is initiated by tissue damage, either as a direct consequence of the burn or indirectly due to cellular damage from ischemia or infection. Toll-like receptors (TLR), expressed mainly by leukocytes, can recognize both exogenous microbial molecules and endogenous ligands leaked from damaged cells. These include peptides, polysaccharides, proteoglycans, nucleic acids, phospholipids, and extracellular matrix degradation products (7). When these TLR pathways are activated, genes are transcribed that are associated with the inflammatory response, such as interleukins (IL)-1, IL-6, and tumor necrosis factor (TNF) α (8). Additionally, cytoplasmic nod-like receptors (NLR) can detect both endogenous and exogenous ligands following damage to cells and cell membranes, with subsequent loss of compartmentalization. NLR stimulation results in the formation of inflammasomes and the production of IL-1 by monocytes and macrophages (9). Burn injury can trigger these inflammatory mechanisms because destruction of the skin barrier permits the entry of multiple micro-organisms into the systemic circulation and destruction of tissue by the burn can cause release of cell breakdown products into extracellular compartments.

3. The Stress Response

While the exact sequence of appearance of the systemic inflammatory and stress responses is not clear, both occur acutely, within the first 24 hours following burn injury. The stress response results in the increased endogenous production of glucocorticoids and catecholamines. The glucocorticoid production as measured by the 24-hour urinary excretion of cortisol indicates a rate of excretion that is 3-8-fold elevated above the normal range (6, 10). These levels decline gradually over the first year post-burn but still can be as high as two-fold elevated at the end of that time (11). Urinary catechol excretion is also elevated but a previous review of catecholamine excretion in pediatric patients with severe burns suggests that sustained elevation in urinary excretion of at least one catecholamine over the first year post-burn occurs in only about 30% of patients (6). As there is an overlap in the effects of inflammatory cytokines and glucocorticoids on bone, it is not certain whether the effects of both are cumulative, proportionate, or disproportionate. Glucocorticoids are known to cause osteoblast and osteocyte apoptosis. Absence of osteoblasts from the bone surface can be seen in iliac crest biopsies after 2-3 weeks (10). However, studies determining precisely how early post-burn the reduction of bone formation occurs have to date not been published. Both glucocorticoids and inflammation can cause oxidative stress, which will be dealt with in section 7.

4. The Hypermetabolic/Catabolic response

The precise initiation of the hypermetabolic/catabolic response to burn injury has not been clarified. However, in order to sustain the systemic inflammatory and stress responses, the body must generate more energy accompanied by increased turnover of ATP. It has been shown that immediately post-burn the resting energy expenditure (REE) in adult patients burned >40% total body surface area on hospital admission is 1.8 times normal, falling to 1.1 times normal at 12 months post-burn (12). In pediatric patients burned >30% total body surface area at two weeks post-burn, the REE is 1.4 times normal, falling to 1.1 times normal at 12 months. If similarly burned pediatric patients are treated from admission with propranolol, their peak REE is only 1.2 times normal and 1.1 times normal at 12 months post-burn (13). Heart rate increases to 160% of unburned individuals by 72 hours following the burn injury and has been reported to remain elevated for up to three years (14). Skeletal muscle is broken down to provide sources of energy, such as alanine (Figure 1), which serves as a substrate for glucose production. The muscle protein liberated by tissue breakdown is also postulated to assist in wound healing (14, 15). Additionally, since skeletal muscle is a major source of glucose uptake by the body, the loss of skeletal muscle and the subsequent development of burn cachexia has been postulated to contribute to post-burn insulin resistance and consequent hyperglycemia (14). Uncoupling of mitochondrial oxidation has recently been identified in skeletal muscle of burned patients along with an increased generation of heat as a contributor to hypermetabolism (16). However, the pathophysiology of the mitochondrial damage is unknown.

Above is the current understanding of these three processes as described in the most recent textbook on burn injury pathophysiology and management (14, 17). What follows is what

has been learned about the musculoskeletal response to burn injury and its implications for the hypermetabolic response.

5. The Musculoskeletal Effects of Burn Injury

Muscle wasting is the most widely known effect of severe burn injury and it is widely attributed to hypermetabolism. As mentioned above, muscle breakdown is believed to serve two purposes: the provision of substrate for gluconeogenesis, namely alanine, and the provision of amino acids to accelerate wound healing (15, 16). There is no discussion as to what actually triggers muscle breakdown. In a hypermetabolic state, we must first review how burns affect the musculoskeletal system as a whole. We will start with bone.

6. Bone

Severe burn injury affects bone in two phases: *acute resorption* that lasts from onset of the acute response (17) up to two weeks post-burn; in children with severe burns, 7% of the lumbar spine bone mass is lost by three weeks post-burn while total body bone mass decreases by 3% at 6 months post-burn (18). The second phase is *reduced formation* leading to an *adynamic state* featuring low bone turnover (6). Thus, there is initially acute bone loss followed by an adynamic state which indicates that lost bone cannot be recovered, at least acutely.

6.1 Bone Resorption

Acute resorption is likely caused by the cytokines IL-1 β and IL-6 (new 6, old 1), both produced by the systemic inflammatory response. In severely burned children, IL-1 β is three-fold elevated in the circulation and serum IL-6 concentration is one hundred-fold elevated (6). When bone is resorbed it liberates calcium, phosphorus, and magnesium. We shall deal with each one separately.

6.1.1 Calcium—The skeleton stores 99% of total body calcium. Resorption releases calcium from the bone into the circulation. Our group has previously shown that *in vitro* human peripheral blood mononuclear cells grown in culture with varying concentrations of medium calcium produced chemokines that varied, either directly or indirectly, with the concentration of calcium in the medium (19). The coefficient of variation ranged from 0.73 to 0.87, indicating a very tight correlation between the two variables (19). Inasmuch as chemokines stimulate the migration of inflammatory cells to a site of inflammation it is possible that the calcium released into the circulation as a consequence of inflammatory bone resorption serves to either prolong or intensify the inflammatory response.

Furthermore, work by Rosol et al (9) has demonstrated that extracellular calcium stimulates the NLRP3 inflammasome, resulting in increased production of IL-1 by the monocytes and macrophages of the innate immune system. In this situation, the parathyroid calcium-sensing receptor (CaSR) was shown to mediate this response.

In burn injury, we have observed a dichotomy in the calcium response depending on the age of the burn patient (new 20, 21). In children and adolescents, IL-1 β (22, 23) and IL-6 (24)

up-regulate the parathyroid CaSR leading to a reduction in the set point for parathyroid hormone (PTH) secretion in response to circulating calcium concentration. Therefore, even lower than normal circulating ionized calcium will suppress PTH secretion leading to hypocalcemic hypoparathyroidism and hypercalciuria (25). This occurrence has been definitively demonstrated in a sheep model of burn injury (26) with a 50% up-regulation of the CaSR mRNA on gel densitometry by 48h post-burn (26). In contrast, adults who are burned to an equivalent extent usually manifest normal to slightly elevated circulating ionized calcium concentrations, with normal to slightly elevated PTH concentrations (20). The implications of this finding are that something in development turns off the ability of the body to up-regulate the CaSR in response to inflammation and that failure to do so may contribute to the persistence of inflammation in the adult and its mitigation in children following a burn. In fact, the post-burn morbidity is considerably higher in adults than it is in children (3) and the regulation of circulating ionized calcium may contribute to this finding. Thus, the putative enhancement of the systemic inflammatory response by circulating calcium may contribute to the persistence of the hypermetabolic response.

6.1.2 Phosphate—Approximately 85% of the body's phosphate is stored in the skeleton (27) and Porter et al (27) calculate that about an additional 10% of the body's phosphate stores are found in skeletal muscle. Following burn trauma there is a significant increase in ATP turnover as well as in other phosphate-bound cofactors due to the increased synthesis and breakdown of proteins associated with hypermetabolism. This leads to the depletion of skeletal muscle stores of phosphate and magnesium. Van Niekerk et al (28) proposed that the phosphate and magnesium released into the blood following bone resorption somehow enhance immune cell function. While this has yet to be demonstrated, it is also possible that the release of phosphate from bone following acute resorption serves to support the amount of substrate needed to sustain ATP turnover in skeletal muscle. Liberated phosphate, then, could help sustain the high rate of muscle protein synthesis and turnover. Additional support for this hypothesis comes from the work of Borsheim et al (29) that demonstrates that the administration of an anti-resorptive drug, pamidronate, to pediatric burn patients who underwent stable isotope studies of muscle protein kinetics had a significantly lower rate of muscle protein synthesis at 30 days post-burn than those who received a placebo. Thus, prevention of bone resorption lowered the rate of muscle protein synthesis, suggesting that elements from bone, such as phosphate, were helping to sustain the high rate of muscle protein turnover. Additionally, as we have previously shown (30), the body's main known phosphaturic hormones, PTH and fibroblast growth factor (FGF)-23, are suppressed, aiding in the conservation of body phosphate to help meet the hypermetabolic demands. It is possible that the brain may play a role in the body's conservation of phosphate during the hypermetabolic phase. With low serum PTH, Mechanick et al (31) noted that urinary phosphate excretion in patients with spinal cord injury was low while they were shown to be hypophosphatemic while a study by Gadisseux et al (32) showed that five patients with traumatic brain injury with serum phosphorus concentrations below 2.0 mg/dl all had urinary phosphate excretion exceeding 100 mg/day. These findings suggest renal phosphate wasting in the presence of traumatic brain injury as opposed to renal phosphate conservation in patients with spinal cord and burn injuries.

6.1.3 Magnesium—An estimated 60% of the body's magnesium stores are found in bone. In metabolism, magnesium binds to ATP and GTP and is a cofactor necessary for the activation of adenylyl cyclase and guanylyl cyclase, phosphofructokinase and phosphocreatine (27). Therefore, magnesium is intimately associated with phosphate metabolism and ATP generation and turnover. Magnesium is also released from bone during resorption and it is possible that the release of magnesium is critical to sustaining the elevated rate of phosphate metabolism following severe burn injury. Of note as well is that pediatric burn patients are likely magnesium depleted. This process starts from the time of burn resuscitation when these patients are treated with Ringer's Lactate solution that is devoid of magnesium (25). Furthermore, as the parathyroid CaSR also recognizes magnesium and up-regulation of the receptor increases magnesium excretion, the most sensitive test we have for magnesium sufficiency, the magnesium loading test, is uninterpretable. Inasmuch as the CaSR is up-regulated (27) and produces hypermagnesuria in that state, magnesium conservation as indicated by reduced urinary magnesium excretion is difficult to document accurately. Thus, up-regulation of the CaSR by inflammatory cytokines may serve as an adaptive response to ameliorate hypermetabolism by preventing magnesium from supporting the sustained rapid turnover of ATP and the high rate of muscle protein synthesis and breakdown. In contrast in adult burn patients the lack of evidence supporting an up-regulation of the CaSR and hypermagnesuria would support a more sustained hypermetabolism.

6.1.4 Muscle Wasting—Inasmuch as muscle wasting may be more related to increased bone resorption than to decreased bone formation, it is appropriate to include this section immediately following that on bone resorption. Thus, another potential side-effect of bone resorption is the liberation of factors in the bone matrix that could affect muscle catabolism, leading to post-burn muscle loss. Waning et al (33) found that in women with breast cancer metastases to bone, transforming growth factor (TGF)- β is liberated from bone and has a paracrine effect on skeletal muscle, targeting the ryanodine receptor, which leads to calcium leakage from the muscle with resulting cachexia. In burns, Borsheim et al (29) found that giving a bisphosphonate once in the first ten days following a severe burn injury in a randomized double-blind controlled trial resulted not only in decreased synthesis of muscle protein but also decreased breakdown with a net positive muscle protein balance in those patients who received the single dose of the bisphosphonate pamidronate compared to those receiving placebo. This anabolic effect was confirmed by demonstrating that muscle fiber diameter in patients receiving pamidronate was significantly greater than in those patients who received a placebo at 30d post-burn and that at 9 months post-burn lower extremity peak torque in those patients who received pamidronate was not different from age and sex-matched normal unburned children while those patients who received placebo had a trend toward significant lower extremity weakness at this time period (28). Preliminary data suggest that the mechanism or mechanisms responsible for these effects are similar to those identified in breast cancer bony metastases (34). Certain factors released during bone resorption likely play a role in the pathogenesis of post-burn cachexia (35). Importantly, these results have been confirmed by several studies both *in vivo* (36, 37) and *in vitro* (38), the *in vivo* studies using bisphosphonates.

Reduced bone formation, in addition to promoting skeletal muscle glucose intolerance may also contribute to reduced muscle mass. Mera et al (39) have reported that osteocalcin stimulates muscle protein synthesis and thus the reduced osteocalcin seen with decreased bone mass (40) would be an impairment to maintenance of muscle mass.

6.2 Bone Formation

It is unclear how early bone formation is reduced after severe burn injury. Initial studies indicated that bone becomes adynamic at about two weeks post-burn in children (6) but that may have been because iliac crest bone biopsies were initially done at two –three weeks post-burn to allow for double tetracycline labeling to quantitate the rate of bone formation. To date, it is not certain what process initiates reduced bone formation. It is possible that the stress response with its increase in endogenous glucocorticoid production is responsible for the reduction (6, 11); it is also possible that pro-inflammatory cytokines such as IL-6 also contribute to this process (6). The significance of the reduction in bone formation for hypermetabolism is not clear, although there may be some physiologic advantage in maintaining a low bone mass to reduce the contribution of products of bone resorption to hypermetabolism. However, reduced bone mass may also contribute to peripheral glucose intolerance inasmuch as serum osteocalcin concentrations are reduced (41) and several investigators (41, 42) have shown that osteocalcin, while produced by osteoblasts, stimulates pancreatic insulin secretion and skeletal muscle glucose uptake.

7. Other Possible Contributory Factors: Oxidative Stress and Vitamin D Deficiency/Insufficiency

Other conditions created by the systemic inflammatory response, sepsis, and the robust glucocorticoid production of the stress response also affect the musculoskeletal system. Chief among these is oxidative stress. Reactive oxygen species are generated by mitochondrial electron transport, beta oxidation of fatty acids, and neutrophil activation (43). Oxygen free radicals affect both bone and muscle metabolism by stimulating the transit of transcription factors in the forkhead box O (FOXO) family to the nucleus in osteoblast precursors, where they bind to β catenin, interfering with new bone formation and in muscle, where they stimulate the ubiquitin ligases atrogin-1 and MuRF-1 leading to an increase in muscle protein breakdown. The net effect of oxidative stress, then, is adynamic bone and muscle wasting. The relative contributions of oxidative stress and bone abnormalities to the maintenance of hypermetabolism is not established.

Similarly, the role of vitamin D in the maintenance of bone and muscle in the post-burn state is unclear. Progressive vitamin D deficiency develops in burn injury due to the combination of failure of burn-injured and surrounding skin to produce normal quantities of vitamin D from its 7-dehydrocholesterol precursor on exposure to ultraviolet B radiation from sunlight (44) and failure of adequate vitamin D supplementation (45) during or following acute burn hospitalization. As vitamin D is reported to play a role in maintaining muscle function (46), restoration of normal circulating concentrations of 25 hydroxyvitamin D may be beneficial to bone and muscle function post-burn.

8. Consequences of Pharmacologic Intervention in Burn-induced Musculoskeletal Dysfunction

As we have described above, single-dose intravenous administration of the bisphosphonate pamidronate during the first ten days post-burn as part of a randomized, double-blind, placebo-controlled study (18) prevented both resorptive bone loss (18) and muscle protein breakdown, resulting in a positive muscle protein balance (29). While the underlying mechanisms supporting this action of bisphosphonates is still being worked out, the end effect is long-term preservation of both bone and muscle mass after burn injury (Figure 1). Does this use of an anti-resorptive agent compromise wound healing, which is postulated to benefit from the breakdown of muscle protein (16)? There is no information currently published on the relative lengths of stay between those patients who received pamidronate and those who received placebo. From a clinical standpoint, no difference has been noted.

9. Future Research Questions in Evaluation of the Overall Musculoskeletal Contribution to Post-Burn Hypermetabolism

The data obtained to date suggest that the musculoskeletal system is affected by the post-burn triad of the systemic inflammatory response, the stress response, and the resulting hypermetabolic state. The age of the burn patient appears to play a role in determining the range of adaptive responses to the burn injury. We currently have evidence that we can prevent both bone resorption and muscle catabolism, which are consequences of the systemic inflammatory, stress, and hypermetabolic responses to burn, yet so far there are absolutely no phase III clinical trials of any anti-resorptive agent given only one time, within the first ten days of burn injury, to demonstrate large-scale benefit to pediatric or adult burn patients without any evidence of toxicity from the single dose. This is the current state of our efforts despite an entire symposium on burns and bisphosphonates that took place at the 2014 International Society for Burn Injuries meeting in Sydney in which these data were presented and the need for phase III studies was reinforced by each speaker. Thus, we cannot as yet prove that the pharmacologic intervention to ameliorate the musculoskeletal response has significant consequences for the triad as a whole. This is a subject for further research. Among the questions that can be asked are the following. If bone mass and muscle mass are maintained following anti-resorptive treatment, what are the consequences for sustaining ATP generation to support hypermetabolism? Are hyperglycemia and insulin resistance improved by the larger mass of skeletal muscle and the normal generation of osteocalcin? What happens to the intensity or duration of the inflammatory response to burns, given the lower rate of calcium entry into the blood? Are there any effects of the preserved muscle mass and strength on the duration of rehabilitation? Could it be shortened? Answers to these questions will go a considerable way toward determining the value of anti-resorptive therapy following burn injury as well as the possible exploration of other anabolic therapies to enhance musculoskeletal function.

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Highlights

Systemic inflammatory response and a stress response follow immediately after a burn injury

Both are related to an acute onset hypermetabolic response which supports the inflammatory and stress responses

The musculoskeletal system is affected by burns resulting in acute bone resorption, muscle wasting and reduced bone formation

Bone resorption liberates calcium to sustain the inflammatory response and phosphate and magnesium to sustain the increased demands for ATP especially in skeletal muscle

Bone resorption also releases muscle catabolic factors such as TGF beta from the bone matrix contributing to muscle wasting

Intervention by anti-resorptives may interfere with the hypermetabolic response possibly reducing burn morbidity and mortality.

Table 1.

Clinical and Laboratory Features of the Post-Burn Triad

Systemic Inflammatory Response	Stress Response	Hypermetabolism
<i>tachycardia</i>	<i>tachycardia</i>	<i>tachycardia</i>
tachypnea	Increased endogenous glucocorticoid production	Muscle wasting
Leukocytosis or leukopenia	Increased sympathetic drive leading to increased catecholamine production	Increased oxygen consumption
hyperglycemia	Increased lipolysis and fatty acid oxidation	Insulin resistance
Increased C reactive Protein		Abnormal skeletal muscle mitochondrial function leading to uncoupling of mitochondrial respiration and heat production
thrombocytopenia		Browning of white adipose tissue
Coagulation disorders		

Modified from Herndon DN Editor, Total Burn Care, Edinburgh, London, Elsevier, Fifth Edition 2018.